
The Pluripotency Factor-Bound Intron 1 of Xist Is Dispensable for X Chromosome Inactivation and Reactivation In Vitro and In Vivo.

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Public Summary:

In the mouse, there is a close coupling between pluripotency and absence of Xist RNA expression: upon differentiation Xist is upregulated to silence one X chromosome in female cells and upon reprogramming Xist coating is lost and the silent X reactivated. Here, we refute the hypothesis that the first intron of the Xist gene is a critical genomic element for the regulation of X chromosome inactivation and reactivation in the mouse system.

Scientific Abstract:

X chromosome inactivation (XCI) is a dynamically regulated developmental process with inactivation and reactivation accompanying the loss and gain of pluripotency, respectively. A functional relationship between pluripotency and lack of XCI has been suggested, whereby pluripotency transcription factors repress the master regulator of XCI, the noncoding transcript Xist, by binding to its first intron (intron 1). To test this model, we have generated intron 1 mutant embryonic stem cells (ESCs) and two independent mouse models. We found that Xist's repression in ESCs, its transcriptional upregulation upon differentiation, and its silencing upon reprogramming to pluripotency are not dependent on intron 1. Although we observed subtle effects of intron 1 deletion on the randomness of XCI and in the absence of the antisense transcript Tsix in differentiating ESCs, these have little relevance in vivo because mutant mice do not deviate from Mendelian ratios of allele transmission. Altogether, our findings demonstrate that intron 1 is dispensable for the developmental dynamics of Xist expression. VIDEO ABSTRACT:

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